PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	27.05.2004
Applicant's or agent's file reference SH-72	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP 03/06453	23.05.2003	01.07.2002

International Patent Classification (IPC) or both national classification and IPC
A61K31/195, A61K31/195

Applicant
SHIMIZU PHARMACEUTICALS CO. LTD. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 01.11.2004

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-15 as originally filed

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9
Inventive step (IS)	Claims	1-15
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: EP-A-0 347 714 (FRESENIUS AG) 27 December 1989 (1989-12-27)

D2: JOERRES, A. ET AL: "In vitro biocompatibility evaluation of a novel bicarbonate-buffered amino acid solution for peritoneal dialysis" NEPHROLOGY, DIALYSIS, TRANSPLANTATION (1997), 12(3), 543-549, 1997, XP002249771

D3: SULIMAN M E ET AL: "Total, free, and protein-bound sulphur amino acids in uraemic patients." NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1997 NOV) 12 (11) 2332-8., XP002249772

D4: BRUNO M. ET AL: "Use of amino acids in peritoneal dialysis solutions." PERITONEAL DIALYSIS INTERNATIONAL, (2000) 20/SUPPL. 2 (S166-S171)., XP009014851

D5: US-B-6 380 1631 (FAICT DIRK ET AL) 30 April 2002 (2002-04-30)

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 is not new in the sense of Article 33(2) PCT.

D2 discloses a novel bicarbonate-buffered amino-acid solution for peritoneal dialysis containing 1% amino acids as the osmotic agent whereby L-taurine is included with 0.799 mmol/l (table 1; abstract). The solution offers improved biocompatibility properties (discussion). Hence, claims 1-8 cannot be regarded as novel.

Likewise, D1 claims an amino-acid solution for peritoneal dialysis containing as well L-taurine in the amino acid mixture from 2 to 8 g/l, especially 4.9 g/l (p. 3; ex. 1) with an osmotic pressure of 300 to 700 mosm/l and a pH of 5.5 to 6.5 (claims). In the case of glucose a two-compartment container is used, otherwise not (p. 5, l. 5-10). Claims 1-9 are novelty-destroyed. The remaining claims are novel since the exact amount of chloride ions is not given in combination with the other electrolytes in D1 (see eg. example 4).

3. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-15 does not involve an inventive step in the sense of Article 33(3) PCT.

Both documents **D1** and **D2** are regarded as being the closest prior art to the subject-matter of claims 1-15.

The subject-matter of claims 1-9 does not differ from this known prior art. Claims 10-15 claim specific amounts of compounds of the peritoneal dialysate not being disclosed in the above mentioned documents.

The problem to be solved by the present invention may therefore be regarded as finding alternatives to the known peritoneal dialysates.

D3 discloses reduced plasma levels of methionine and taurine concentrations (table 2; p. 2335, col. 2, par. 2) in patients receiving continuous ambulatory peritoneal dialysis (CAPD) and haemodialysis (HD). The addition of taurine to conventional therapy in these patients is suggested since low plasma levels of taurine are associated with dilated cardiomyopathy and since chronic uraemic patients exhibit a higher incidence of cardiovascular disease (p. 2337, col. 1, par. 3-4).

D4 as well discloses reduced plasma levels of taurine and other alterations in plasma in CADP patients and the role of taurine in regulating calcium ion fluxes (p. S166, col. 2, par. 4; p. S167, col. 1). The use of amino acids results in nutritional benefits whereby the risk of acidosis should be taken into consideration; therefore the recent formulations use up to 40 mEq/l lactate (p. S168, col. 2 - S169, col. 1). Furthermore, it is stated that Oreopoulos et al first used amino acids instead of glucose as an osmotic agent in patients on CAPD (p. S167, col. 2, par. 6).

D5 claims peritoneal dialysis solutions with polypeptides whereby very similar amounts of electrolytes and alkalizers and pH ranges as in the previous application are given (col. 13; claims). Taurine is not mentioned.

In view of D3 and D4, the skilled in the art would be prompted to use taurine instead of other amino acids in a dialysate solution in order to increase the low plasma level of dialysed patients as well as an osmotic agent.

Hence, claims 10-15 cannot be regarded as involving an inventive step since said amounts of electrolytes and alkalizers are known in the art for the preparation of peritoneal dialysis solutions.